UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/718,998	11/22/2000	Cary L. Queen	11823-002660US	4998

20350 7590 12/03/2004

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/718,998	LANDOLFI ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P ri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-209* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) *135,138,142,149-152,155,159,160,163,169,172,181,188,191 and 193-196* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

ontinuation of Disposition of Claims: Claims rejected are 108-134,136,137,139-141,143-148,153,154,156-158,161,162,164-68,170,171,173-180,182-187,189,190,192 and 197-209.

DETAILED ACTION

Election/Restrictions

1. The amendment filed June 28, 2004 is acknowledged.

Claims 108-209 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Withdrawn:

3. The objection to the specification is withdrawn. A substitute specification has been entered into the file.

4. The objection to the specification for failure to comply with the Sequence Rules is withdrawn in view of the submission filed June 28, 2004.

5. The rejection of claims 108-111, 113-115, 119-124, 133-169, 208 and 209 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claims.

6. The rejection of claims 109, 111, 117, 120, 128, and 131 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants' persuasive arguments.

7. The rejection of claims 108-135, 137-172, 174-191, 193-201, 203-209 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized immunoglobulins having affinities within 2- to 4-fold the affinity of the parent antibody, does not reasonably provide enablement for any humanized immunoglobulin having affinities much higher than that of the parent immunoglobulin is withdrawn in view of the amendment to the claims.

8. The rejection of claims 133, 138, 142, 148, 150, 158-162, 164, 166-168, 170, 175, 177, and 199 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants' persuasive arguments.

9. The rejection of claims 116-132 under 35 U.S.C. 102(e) as being anticipated by Huston (U.S. Patent 5,476,786; issued Dec. 19, 1995; effective filing date May 21, 1987) is withdrawn upon further consideration.

Rejections Maintained:

Double Patenting

Applicants' remarks concerning the double patenting rejections are acknowledged. Applicant does not acquiesce in the merits of the rejection, but is prepared to file a terminal disclaimer on indication of other wise allowable subject matter.

10. The rejection of claims 108-132 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18, 20 and 21 of U.S. Patent 6,180,370 (for claims 108-115 of instant application); claims 10, 13, 17-21, 28-30 of U.S. Patent 6,180,370 (for claims 116-124 of instant application); and claims 1, 2, 3, 5, and 25-27 of U.S. Patent 6,180,370 (for claims 125-132 of instant application) is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other.

11. The rejection of claims 108-124 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, and 9-11 of U.S. Patent 5,530,101 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other.

12. The rejection of claims 108-132 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 7-20 of U.S. Patent 5,693,762 is

maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other.

13. The rejection of claims 108-124 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent 5,585,089 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other.

New Grounds of Rejection:

14. Claims 125-132 and 198-209 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 125 and 129 are indefinite because of the phrase "heavy chain variable region framework whose sequence is a consensus sequence of human heavy chain variable region framework sequences". This phrase may be interpreted as a structure having a concatenation of many heavy chain variable region frameworks.

Claim 198 is indefinite because of the phrase "the acceptor immunoglobulin heavy chain variable region framework is a consensus sequence of human immunoglobulin heavy chain variable region frameworks". This phrase may be interpreted as a structure having a concatenation of many heavy chain variable region frameworks.

15. Claims 118, 121, 136, 173, 182, 192, and 202 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 118, 121, 136, 173, 182, 192, and 202 recite the limitation that the humanized immunoglobulin binds to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, which is a limitation that appears in the independent claims from each of these claims depends.

Claim Rejections - 35 USC § 102

16. Claims 108, 110, 112-115, 133, 134, 136, 137, 139-141, 143-148, 153, 154, 156-158, 161, 162, 164, 165-168, 170, 171, 173-180, 182-187, 189, 190, 192 and 197, 208 and 209 are rejected under 35 U.S.C. 102(a) as being anticipated by Riechmann (Riechmann, L. et al., Nature, 332: 323-327, 1988, March).

The claimed inventions are drawn to humanized immunoglobulins that specifically bind to an antigen with an affinity constant within about four-fold that of the donor immunoglobulin, wherein the humanized immunoglobulins comprise at least three amino acids from the donor immunogloublin heavy chain framework outside the Kabat CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy chain framework; or wherein the humanized immunoglobulins comprise an amino acid from the donor immunglobulin framework outside the CDRs that replaces the corresponding amino acid in the acceptor immunogloublin framework at selected positions. In some embodiments of the claimed invention, the donor amino acids are immediately adjacent to CDRs, or capable of interacting with CDRs, or are typical at their

positions for human immunoglobulin sequences, and the replaced amino acids are rare at their positions for human immunoglobulin sequences. The humanized immunoglobulin may be an antibody tetramer, Fab, or (Fab')2, may be substantially pure, or may be comprised within a pharmaceutical composition in a pharmaceutically acceptable carrier.

The limitation that the humanized immunolgobulins comprise "amino acids from the donor immunglobulin" that "replace the corresponding amino acids in the acceptor immunoglobulin" renders the claim a product-by-process claim. Therefore, if the prior art teaches a humanized immunoglobulin structure that comprises amino acids that are the same in the acceptor as in the donor at positions that correspond between the acceptor and the donor, and the positions are outside CDRs, and the positions are immediately adjacent to CDRs, or capable of interacting with CDRs, or are typical at their positions for human immunoglobulin sequences, that structure reads on the claimed immunoglobulin despite the fact that the method of making the structure in the prior art does not include a process step of replacing an acceptor amino acid with a donor amino acid. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The

product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.) MPEP 2113.

Riechmann teaches the claimed immunoglobulins because Riechmann teaches a humanized antibody having an affinity that is within four-fold that of the donor immunoglobulin (see page 324, Figure 1 and page 326, col. 1, 1st full paragraph, and Table 1, compare RaVHCAMP with HuVHCAMP(Ser27-Phe)). Riechmann's antibody comprises at least three amino acids that are the same as the amino acids of the donor at positions that are immediately adjacent to one of the CDRs or are capable of interacting with the CDRs (The specification teaches at column 15, line 20-21, that positions L2, L48, L64 and L71 of the light chain, and H26-H30 and H94 of the heavy chain are amino acids that are known to be capable of interacting with CDRs.). Riechmann teaches purification of the humanized antibody into PBS (phosphate buffered saline, see legend of Figure 4). Therefore, for claims 108, 110, and 112-115, Riechmann teaches humanized immunoglobulins that are the same as that claimed because Riechmann's humanized antibody comprises amino acid residues at positions H26-H30, H36, H49, H66, H94 and H103 that are the same as residues in the corresponding positions of the donor antibody.

For claims 133, 134, 136, 137, 139-141, 143-148, 153, 154, 156-157, 161, 162, 164, 165-168, 208 and 209, Riechmann's antibody is the same as that claimed because Riechmann's antibody comprises amino acid residues at positions L9, L13, L36, L41, L48, L49, L63, L70, L71, L79, H49, H66, H68, H72, H86, H87, H91, H94, H103, H104, and H105, that are the same

as that in the corresponding positions of the donor antibody, and are residues that are either adjacent to a CDR or are capable of interacting with the CDRs.

For claims 170 and 173-177, Riechmann's antibody is the same at that claimed because Riechmann's antibody comprises amino acid residues at positions H49, H66, H94 and H103 that are the same as that in the corresponding positions of the donor antibody, and are residues that are adjacent to a CDR.

For claims 178-180, 182-186 and 187, Riechmann's antibody is the same as that claimed because Riechmann's antibody comprises amino acid residues at positions L36, L48, L49, L70 and L71 that are the same as that in the corresponding positions of the donor antibody and are capable of interacting with CDRs.

For claims 189, 190, 192, and 197, Riechmann's antibody is the same as that claimed because Riechmann's antibody comprises an amino acid residue at position H72 that is the same as that in the corresponding positions of the donor antibody and is capable of interacting with CDRs.

17. Claims 116, 118, 119, 121-124, 198-200, 202, 204, and 207 are rejected under 35 U.S.C. 102(a) as being anticipated by Riechmann (Riechmann, L. et al., Nature, 332: 323-327, 1988, March) as evidenced by Waldmann (U.S. Patent, 5,846,534; issued Dec. 8, 1998; effective filing date Oct. 12, 1989).

The claimed inventions are drawn to humanized immunoglobulins that comprise a "consensus framework" or a "consensus heavy chain". The specification fails to define the term "consensus framework" or "consensus heavy chain". In addition the specification fails to

describe how many sequences are included in a comparison to determine consensus for a framework or a heavy chain. Applicants have argued that in the absence of a definition, that the terms "consensus framework" or "consensus heavy chain" should take on their customary meanings as given by persons experienced in the field, and cites a text book definition relating to a consensus sequence found in the promoter region of many genes, where a consensus nucleotide sequence found within the promoter region of many genes is a sequence that comprises the most frequently occurring nucleotides. Applicants assert that in the case of "consensus framework" or "consensus heavy chain", one experienced in the art would understand that a "consensus framework" or a "consensus heavy chain" would be a framework or a heavy chain comprising amino acid sequences in which each amino acid is an amino acid that is the most frequently occurring amino acid in a family of related sequences. This argument is not found persuasive because absent a definition, claim terms may be given their broadest reasonable interpretation. The specification provides no definition of the term "consensus framework" and provides no examples of structures that are "consensus frameworks". What the specification does provide is a contemplation of frameworks that contain substitutions of a "rare" amino acid with a "typical" amino acid, where the "typical" amino acid is not the same as that of the donor residues (col. 15, line 56 – col. 16, line 3, in parent U.S. Patent 6,180,370). The citation of a reference containing a definition for "consensus sequence", where the definition is for a nucleic acid sequence found within a promoter region of a gene, is not adequate to demonstrate that the examiner's position is unreasonable, where the examiner is taking the position that, in light of the teachings of the specification, a consensus framework my be broadly defined as including those frameworks that contain some amino acid residues that are commonly found in many other immunoglobulin

frameworks. Therefore, it is not clear that applicants' interpretation of the term "consensus framework" may be used to limit the term to a framework where both the heavy and the light chain have an amino acid sequence, where at each position in the sequence the amino acid is the most common amino acid of a given group of heavy and light chains.

In the case of claims 116, 118 and 198, the claims are drawn to humanized immunoglobulins comprising a consensus framework (claim 198 is interpreted to comprise a "consensus framework" because the phrase "consensus sequence of human immunoglobulin heavy chain variable region frameworks" is unclear). Riechmann, as evidenced by Waldmann clearly teaches a humanized antibody that comprises a consensus light chain, because the light chain of Riechmann is a light chain that is based on REI, and as evidenced by Waldmann, is a sequence that incorporates human framework regions identical to the most common residue in each position in the Kabat alignment of the human kappa subgroup I, except for residues 97-108; see Waldmann, col. 7, line 37 – col. 8, line 16). The sequence of the framework region of the light chain in Figure 3 of Waldmann is the same as the sequence of the framework region of the light chain in Riechmann. Therefore, Riechmann teaches a humanized antibody having a consensus framework, because Riechmann teaches a humanized antibody having a consensus light chain.

Applicants have argued that even if one agrees with the interpretation that Riechmann's light chain is a consensus light chain, that a consensus framework requires the presence of both a consensus light chain and a consensus heavy chain. This is not persuasive because there is no definition provided in the specification that limits a consensus framework to a framework having both a consensus heavy and light chain. Additionally, applicants' arguments that Riechmann

fails to teach a consensus heavy chain are also found to be unpersuasive. Riechmann teaches a heavy chain which was derived from a NEW heavy chain, except that it contains a mutation at Kabat position 27 from serine to phenylalanine, where the serine is less common in human antibodies and phenylalanine is more common. Additionally, Riechmann's heavy chain contains a proline at position 41 and a leucine at position 45, where proline-41 and leucine-45 appear to be the common amino acid residues for each of these positions for most heavy chain sequences (see page 325, 2nd col., and Figure 1a, upper line, positions 41 and 45). The NEW heavy chain may contain other residues that are common for most human heavy chains, and therefore there may be further basis for interpreting the heavy chain of Riechmann's humanized antibody as comprising a consensus heavy chain.

With respect to the limitation present in claims 116, 119 and 198, that the claimed humanized immunoglobulins must also comprise amino acids from the donor immunoglobulin variable region framework outside the CDRs that replace the corresponding amino acids in the acceptor immunogloublin, wherein each of these said donor amino acids is capable of interacting with the CDRs, Riechmann's humanized antibody meets this limitation, because this limitation is interpreted as a product-by-process limitation. Riechmann's humanized antibody comprises many amino acid residues that are the same as the residue of the donor for several positions. For example, in the heavy chain H26-H30, H36, H49, H66, H94 and H103 are the same in the humanized as in the donor and these residues are known to be capable of interacting with CDRs. Similarly in the light chain, L36, L48, L49, L70 and L71, are the same in the humanized as in the donor and these residues are known to be capable of interacting with CDRs.

Therefore, Riechmann, as evidenced by Waldmann, teaches the claimed humanized immunoglobulins.

Conclusion

Claims 108-134, 136, 137, 139-141, 143-148, 153, 154, 156-158, 161, 162, 164, 165-168, 170, 171, 173-180, 182-187, 189, 190, 192 and 197-209 are rejected. Claims

Claims 135, 138, 142, 149-152, 155, 159, 160, 163, 169, 172, 181, 188, 191, 193-196 are objected to for depending from a rejected claim.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
November 23, 2004

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER
11/29/2004

JASEMINE C. CHAMBERS
DIRECTOR
TECHNOLOGY CENTER 1600